New dual recognition mechanism discovered in tuberculosis

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One third of the world's population is infected with Mycobacterium tuberculosis (MTB), which leads to tuberculosis (TB), a leading cause of death world-wide. A new discovery, led by a team of researchers from Case Western Reserve University School of Medicine, offers hope for new approaches to the prevention and treatment of TB. The team's discovery of a novel mechanism that may contribute to immune recognition of MTB is published in the September issue of *Nature Structural and Molecular Biology*.

Most individuals with TB recover from the initial infection and become asymptomatic, but the bacterium persists for years, surviving largely inside macrophages, a type of cell that resides in the immune system. This presents a public health problem in that TB can reactivate and cause serious disease or death. Researchers and physicians know the body's immune system is capable of containing the infection but not curing it completely. It begs the question: "How does the organism survive in the human immune system for so many years?"

For the past 15 years, Drs. Clifford Harding and W. Henry Boom of Case Western Reserve have been seeking the answer to this question. Their work indicated that MTB can inhibit the ability of macrophages to stimulate infection-fighting immune responses, and they identified that a protein on macrophages called Toll-like receptor 2 (TLR2) is involved in this immune evasion mechanism. TLR2 seems to be a two-edged sword in the complex immune response to MTB, as it helps some immunity mechanisms and inhibits others. Understanding the balance of these

effects and the role of TLR2 may provide insights to design therapies for TB.

"Understanding how MTB interacts with the immune system and how it can both activate and inhibit the immune response is critically important for the design of the next generation of TB vaccines. The persistence of infection is dependent on MTB's ability to manipulate our immune system to its advantage. The paradox here is that the MTB molecule, LprG, stimulates TLR2, one of the major receptors we have to identify disease-causing microorganisms. In this case, too much stimulation through TLR2 actually favors MTB by causing parts of the immune response to shut down," explains W. Henry Boom, MD, professor of medicine and director of the Tuberculosis Research Unit at Case Western Reserve School of Medicine.

The new studies show that the potency of LprG to induce these responses is explained by its combination of two mechanisms to activate TLR2: first, by directly stimulating TLR2 and, second, by serving as a carrier to deliver other molecules that stimulate TLR2. This dual mechanism may drive stronger regulation of immune responses by MTB, and future vaccine development may be enhanced by designing approaches to use such mechanisms. Furthermore, the work indicates that LprG contributes to the assembly of the bacterial cell wall, suggesting that it may be possible to develop molecules to interfere with LprG function and potentially serve as new antibiotics to fight TB. The development of new antibiotics is an increasingly important goal, since resistance to existing antibiotics is becoming widespread.

A multi-institutional partnership contributed to the overall success of this research initiative. Two important collaborative groups were led by James C. Sacchettini, PhD, Texas A&M University and D. Branch Moody, MD, Harvard Medical School. In addition, the project was spearheaded by Michael G. Drage and Nicole D. Pecora, two Case

Western Reserve students in the MSTP Program, granting dual MD and PhD degrees, in collaboration with Jennifer Tsai, a graduate student in Dr. Sacchettini's group.

"Our research team is composed of several collaborative groups that each contributed key components to this project. The synergistic way in which the team interacted was a perfect example of scientists working together to advance the study of a disease that detrimentally impacts the lives of so many across the globe. We look forward to continuing to advance this research together," says Clifford V. Harding, MD, PhD, professor and interim chair of pathology at Case Western Reserve School of Medicine.

As they look to the future, the research team will work to gain a better understanding of immune responses in TB and hopefully design approaches to treat the deadly disease, including antibiotics or immunotherapies. Continued work will include study of the mechanism of immune-evasion by MTB with the hope of finding ways to reverse this mechanism so that it no longer causes a persistent infection.

Provided by Case Western Reserve University

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